PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/052626	22.10.2004	28.10.2003

International Patent Classification (IPC) or both national classification and IPC
C07D307/87, C07C255/50, C07F3/02

Applicant
ADORKEM TECHNOLOGY SPA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-22
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. **Re Item I** ***(Basis of the report)***

Reference is made to the following documents:

D1: EP-A-0 171 943 (LUNDBECK & CO AS H) 19 February 1986 (1986-02-19)
D2: WO 02/060886 A (HILDEN LEIF ;GRUMANN ARNE (FI); HUUHTANEN TUOMAS (FI); ORION CORP) 8 August 2002 (2002-08-08)
D3: WO 03/029236 A (PHARMACHEM TECHNOLOGIES LTD ;DAPREMONT OLIVIER (US); MALIK A ASLAM) 10 April 2003 (2003-04-10)
D4: WO 98/19512 A (PETERSEN HANS ;BREGNEDAL PETER (DK); BOEGESOE KLAUS PETER (DK); LU) 14 May 1998 (1998-05-14)
D5: US-B1-6 229 026 (PETERSEN HANS) 8 May 2001 (2001-05-08)

2. **Re Item V** ***(Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement)***

2.1 Subject-matter

Present claims 1-20 relate to a process for the preparation of the known antidepressant 'Citalopram' characterized by

- treating 5-cyanophthalide with
- a mixture of two Grignard reagents (4-fluorophenyl magnesium halide and 3-dimethylaminopropyl magnesium halide)
- followed by acidic treatment, treatment with phosphine or with a labile ester forming group and a base.

Present claims 20 and 21 relate to an diphenyl-intermediate.

2.2 Novelty

Documents D1-D5 disclose methods for the preparation of 'Citalopram' characterized by

a) treating a phthalide derivative with a first Grignard reagent (4-fluorophenyl magnesium halide) followed by
b) reacting the obtained intermediate with a second Grignard reagent (3-dimethylaminopropyl magnesium halide)

Accordingly, the subject-matter of present claims 1-20 is novel over D1-D5 in

view of the instantaneous one-pot-reaction of the phthalide derivative with two Grignard reagents.

As far as novelty of the subject-matter of claims 21 and 22 is concerned, the following is stated: D1 discloses the conversion of the di-magnesium halide (see D1, compound of formula VI) to the corresponding diol (see D1, compound I) by acidic hydrolysis. However, no information is given in D1 about which "MgHal"-group is hydrolysed first or whether both "MgHal"-groups may be hydrolysed at the same time. Consequently, no means are provided by D1 how to obtain the mono-alcohol of claims 21 and 22.

The subject-matter of claims 21 and 22 fulfills the requirements of novelty.

2.3 Inventive step

Document D1 is considered as closest prior art. This document discloses on pages 3-4 and claim 1 a route for the preparation of 'Citalopram' starting from 5-cyanophthalide via subsequent treatment with two Grignard reagents.

In view of this document, the problem to be solved can be regarded as the provision of a further process for the preparation of 'Citalopram'.

The solution provided consists in a process according to claim characterized by reacting the 5-cyanophthalide known from D1 with a mixture containing two Grignard reagents representing a simultaneous reaction instead of a subsequent procedure known from D1.

Based on the available prior art which all teach a subsequent conversion of the phthalide it could not be predicted that a simultaneous one-pot reaction provides the desired product 'Citalopram' as shown in example 3 of the present application.

The subject-matter of claim 21 and 22 is considered as an **intermediate** used in an inventive process The inventivity is therefore derived from its contribution to the inventive process.

The requirements of inventive step are fulfilled.

3. Re Item VIII *(Certain observations on the international application)*

3.1 Claim 22 is wrongly numbered.

3.2 Claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The following functional statements do not enable the skilled person to determine which technical features are necessary to perform the stated functions:

".. or with a labile ester forming group and a base"

The relative term "labile" used in claim 1 has no well-recognised meaning and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.